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Enterocolitis: an adverse event in refractory epilepsy patients treated with levetiracetam?

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***Introduction*:** Levetiracetam (LEV) is a recently marketed novel anti-epileptic drug with a promising efficacy and safety profile. In this report we describe two patients who presented with enterocolitis and discuss the possible relationship with concurrent LEV intake.

***Patients*:** In two patients, LEV was initiated to control refractory complex partial seizures (CPS). The first patient was treated with 1500 mg/day and complained of abdominal pain and weight loss 6 months later. Internal examination and colonoscopy revealed a punctate colitis. The second patient presented with bloody stool 1 month after LEV initiation. Colonoscopy showed punctate colitis. In both patients gastrointestinal symptoms disappeared following tapering of LEV.

***Discussion*:** There are no reports in the literature describing colitis related to LEV intake. Three possible mechanisms of action are discussed. Colitis may be part of a hypersensitivity syndrome caused by LEV. Pharmacodynamic interactions with other anti-epileptic drugs, for example, carbamazepine may play a role. A haematological adverse event is another possibility since piracetam, a related molecule, has a known impact on erythrocytes and platelets.

***Conclusion*:** The close temporal relationship between initiation of LEV intake, symptomatic colitis and clinical improvement following LEV tapering, suggests that colitis may be a possible and previously undescribed adverse effect of LEV.

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Key words: levetiracetam; adverse events; refractory epilepsy; colitis.

INTRODUCTION

Epilepsy is the second most common chronic neurological condition after migraine, affecting between 0.5 and 2% of the population.[1] Medical treatment with one or more first-line antiepileptic drugs (AEDs) will render a majority of patients seizure free.[2] However, a recent 3-year study estimated that 44% of patients with epilepsy fail to achieve seizure freedom, even with medication.[3] This high number emphasizes the need for additional research and progress in epilepsy treatment. Contemporary treatment options for these patients include continued polytherapy with or without novel AEDs, epilepsy surgery, or vagus nerve stimulation.

Recently, several novel AEDs have been added to the pharmacotherapeutic armamentarium.[4,5] One of these drugs is levetiracetam (UCB L059, "Keppra", LEV), a derivative of the nootropic drug piracetam[6,7] with a wide spectrum of anticonvulsant effects in animal models for different types of epileptic seizures.[8–12] Although the mechanism of action has not been fully elucidated, the drug does not appear to act at any recognized site of AED activity such as GABA-receptors or sodium channels.[13] Instead, in vitro studies suggest a specific binding site in the CNS membranes.[14] Apart from its antiepileptic effect there is evidence that LEV may also exhibit antiepileptogenic properties.[15]

LEV also has a favorable pharmacokinetic profile. In humans, LEV is rapidly and completely absorbed after oral administration; there is no effect of food intake on the extent of absorption. Peak LEV serum concentrations occur approximately 1 h after administration in healthy young volunteers. Unlike some other AEDs, LEV is not metabolized in the liver; instead, it is transformed by enzymatic hydrolysis of

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the acetamide group in the blood to inactive metabolites. LEV and its major metabolite are renally eliminated, with approximately 66% of a dose excreted unchanged. Both compounds circulate largely unbound (<10% bound) to plasma proteins. The half-life of 6–8 h in adults permits twice-daily dosing.[4,16,17]

In December 1999, the Food and Drug Administration (FDA) approved LEV for adjunctive therapy in the treatment of partial-onset seizures in adults with epilepsy.

LEV initiated at doses of 2000 or 4000 mg daily without titration is well tolerated and effective as add-on therapy in patients with partial and/or generalized seizures.[18] The most common side effects are asthenia, dizziness, flu-like syndrome, headache, rhinitis and somnolence.[17] Number needed to treat analysis shows that LEV belongs to the group of most effective AEDs.[19] Recent literature suggests that LEV may be even more effective for certain subpopulations, for example, late-onset partial epilepsy[20] and early after failed epilepsy surgery.[21]

In Belgium, LEV became available for use in patients mid 2001. Patients taking one but no more than two other AEDs and with at least one partial seizure and no more than 14 partial seizures per month were included in the Safety of Keppra as Adjunctive Therapy in Epilepsy (SKATE) trial. For patients taking more than two AEDs or with a higher seizure frequency, LEV was made available by UCB Belgium in compassionate use until reimbursement was granted in July 2002.

Recently, a report speculated on a possible haemorrhagic diathesis in patients treated with LEV and undergoing resective surgery for refractory epilepsy.[22]

Since 2001, 85 patients have been treated with LEV as add-on therapy at the Reference Centre for Refractory Epilepsy in Ghent University Hospital, Belgium. In 65 patients, comprehensive follow-up information was available; the other 20 patients only recently received LEV. Thirty patients out of 65 (46%) reported one or more adverse events. Behavioural/emotional problems (11 out of 65 patients, 17%) and asthenia/somnolence (17 out of 65 patients, 26%) were the most commonly reported individual adverse events. One patient reported dizziness, one reported a nose bleed, one female patient complained of menorrhagia and three patients reported diplopia.

Here we describe two patients who presented with abdominal symptoms while being treated with LEV and discuss the possible relationships between this side effect and exposure to LEV.

Worldwide, 140,674 patient years of LEV treatment were reached in July 2002. At this time (January 2003), the number of patient years is estimated to have reached 200,000. 150,000 patient years is accepted to be the limit to reveal uncommon (exceptional) side effects. Post-marketing studies have not reported any uncommon side effects.

CASE-REPORT #1

JDL is a 63-year-old, right-handed woman with complex partial epilepsy since 1993. At the age of 10, the patient had a head trauma with a short-lasting loss of consciousness. At age 36, she underwent a removal of the uterus and ovaries because of suspected malignancy. The patient suffered from migraine and also had a history of two stomach ulcers, one complicated with a bleeding that was conservatively treated, and two tapeworm infections.

Habitual seizures occur typically after a migraine attack and are followed by an episode of acute depression. Seizures are commonly preceded by an epigastric aura followed by a reduced level of alertness, impaired speech and ambulatory automatisms. Seizures often occur in clusters of 1 day every month. Initially the patient was treated with carbamazepine and sodium valproate. Subsequent drug trials with newer AEDs such as topiramate (200 mg daily) and lamotrigine (250 mg daily) failed because of unacceptable side effects. Both were discontinued because of pruritus and a rash.

The patient presented at the epilepsy clinic in the Reference Centre for Refractory Epilepsy at Ghent University Hospital in March 2000 and was included in a presurgical evaluation protocol. During video-EEG monitoring, the patient had a flurry of complex partial seizures (CPS) with clear-cut temporal lobe semiology. The ictal EEG showed left frontotemporal rhythmical theta recruitment at the clinical onset. The interictal EEG showed left frontotemporal spikes. Magnetic resonance imaging (MRI) showed discrete bilateral hippocampal signal changes on T2-weighted images. FDG-PET (positron emission tomography) revealed a left frontotemporal hypometabolism. Neuropsychological evaluation revealed memory impairment suggestive of right temporal involvement. Due to the bilateral abnormalities on structural imaging, invasive video-EEG monitoring with bilateral depth electrodes was planned following Wada-testing to assess language dominance and memory performance. She failed the Wada-test, possibly due to multiple seizures the night before and refused to retake the test. Ultimately the patient chose to halt further diagnostic procedures and to continue with AED treatment.

At that time, her medication consisted of clonazepam (2 mg/day) and carbamazepine (800 mg/day). She reported a seizure frequency of three to seven CPS per month. Clinical investigations showed no signs of drug intoxication. Tiagabine (30 mg/day) was added to the AED regimen but had to be tapered

shortly after initiation due to pruritus, stomach ache, dizziness and headache. In February 2002, she was included in the SKATE study and 1000 mg LEV was added to her AED regimen. At the time of the second follow-up consultation in April 2002, she was completely seizure-free but complained of tiredness and depression. From a pre-study weight of 138 pounds, she had lost 18 pounds over this period of 2 months. There were no other associated systemic complaints at this time and no signs of any drug toxicity on clinical neurological examination and paraclinical investigations (RBC: $4.26 \times 10^6\ \mu l^{-1}$, Hg: 13.2 g/dl, platelets: $173 \times 10^3\ \mu l^{-1}$, gamma-GT: 34 U/l, CRP 1.7 mg/dl). Sertraline was added to her medication regimen and LEV was reduced to a dosage of 500 mg/day. After being seizure-free for more than 15 weeks with LEV treatment, she described a new cluster of seizures at the consultation in May 2002. The dose of LEV was increased to 1000 mg daily.

In August 2002, she reported five short-lasting CPS over a period of 4 months. Here-upon, the dose of LEV was increased further to 1500 mg daily. Because of fatigue, clonazepam was discontinued. She also reported stomach ache and continuing weight loss despite a good appetite in the previous weeks. The patient was referred to the Gastro-enterology department. She complained of pain that was localized in the right hypochondrium, spreading to the entire upper abdomen and increasing after a meal. During the last week she had experienced minor constipation. Stool had a normal colour and consistency and no macroscopic blood involvement. Clinical examination displayed a non-tender abdomen with normal bowel sounds. Blood pressure was 140/90 mmHg and pulse rate was regular at 60 beats/min. There was a normal palpation of breasts and thyroid. Laboratory examination showed normal results (sedimentation rate 1° per hour: 1 mm/unit, RBC: $4.29 \times 10^6\ \mu l^{-1}$, Hg: 13.4 g/dl, platelets: $198 \times 10^3\ \mu l^{-1}$, gamma-GT: 42 U/l). Other liver function tests (LFT) including PTT, glucose level and thyroid tests were normal except for a slightly increased infectious parameter (CRP: 0.7 mg/dl). Abdominal CT scanning showed hypodense regions in the liver compatible with benign cysts. There was no evidence for atherosclerotic disease of the abdominal vessels. Gastroscopy yielded normal findings. Colonoscopy revealed a punctate colitis at the level of the ileocaecal region. Several biopsy specimens had a histologically normal aspect. In particular, no eosinophylic infiltrates could be found.

After a reduction of the dosage of LEV, symptoms immediately disappeared and did not re-occur. The patient is currently (January 2003) on 1000 mg and has reported the occurrence one CPS during the previous 3 months.

CASE-REPORT #2

WDS is a 32-year-old, heterosexual male with simple and CPS and sporadic secondary convulsions since the age of 18, secondary to herpes encephalitis. Seizures typically occur in clusters of five to six seizures in 2 days alternating with periods of relative seizure freedom.

The patient underwent a comprehensive presurgical evaluation at Ghent University Hospital in 1998. All performed examinations (video-EEG monitoring, interictal FDG-PET, optimum NMR, neuropsychological testing and invasive EEG studies) suggested right-sided medial temporal lobe seizure onset. Accordingly, a right temporal lobectomy and hippocampectomy was performed in May 1999. One year after surgery, he had a seizure frequency reduction of more than 90%. He still experienced some short-lasting episodes of staring, salivation and severe dizziness. LEV (1000 mg/day) was added in February 2002 to the AED regimen of carbamazepine 800 mg, sodium valproate 1500 mg and clonazepam 2 mg. The dosage of LEV was increased with increments of 500 mg/week. At this time, laboratory test values (blood chemistry, haematology, glucose, lipids, hormones, drug monitoring and enzymes) were completely normal apart from elevated lipids (total cholesterol 246 mg/dl, TG 388 mg/dl) and gamma-GT (130 IU/l).

In May 2002, he reported five short-lasting episodes of dizziness. He also complained of a bloody stool during 1 week for which he received medication from his general practitioner intended for haemorrhoids. At the time of the next consultation, in September 2002, he described two generalized epileptic seizures, reoccurring episodes of bloody stool with no apparent triggering factors and fatigue. Laboratory tests at that time were normal (RBC: $5.16 \times 10^6\ \mu l^{-1}$, platelets: $196 \times 10^3\ \mu l^{-1}$, normal LFT including PTT, therapeutic carbamazepine level: 7.6 μg/l, subtherapeutic valproate level: 40.4 μg/l and slightly elevated creatinine concentrations: 1.10). The patient denied the intake of antibiotics, NSAIDs or salicylic acids, and no enemas were performed. Gastro-enterological examination revealed a normal clinical status with a non-tender abdomen and normal bowel movements. Proctological examination was negative and a colonoscopy was performed which revealed a punctate colitis. Six biopsy samples were histologically normal. No specific infiltrates were found.

Because of the reoccurring episodes of bloody stool and associated somnolence, LEV was discontinued. At the latest follow-up consultation in October 2002 he reported no further change in seizure control and no more generalized tonic–clonic insults. There was a complete disappearance of the bloody stool after LEV termination.

DISCUSSION

Results of pre-clinical studies provide no evidence for a carcinogenic, mutagenic, or teratogenic potential of LEV.[12] Cereghino et al. studied patients with uncontrolled partial seizures in a double-blind, randomised clinical trial. Of 199 patients receiving LEV, treatment-emergent adverse events with an incidence higher than placebo were: asthenia, dizziness, flu syndrome, headache, infection, rhinitis and somnolence. 5.1% of patients reported abdominal pain versus 10.5% in the placebo group.[17] In another European multi-centre, double-blind, randomised, placebo-controlled trial in which add-on LEV therapy was compared to placebo in 324 epilepsy patients, the most frequent adverse events were similar: asthenia, headache, accidental injury and somnolence. No clinically relevant changes compared to baseline values were found for any monitored parameter (blood chemistry, haematology, urine analysis, vital sings, ECG). Abdominal pain was reported in 5.7% of the patients receiving LEV 1000 mg/day versus 3.6% in the placebo group.[23] A recent review including 3347 patients exposed to LEV summarized that LEV is well tolerated and safe and that the overall incidence of adverse effects in the LEV groups was only slightly higher than in the placebo groups.[24]

In view of the close temporal relation in our patients between the start of LEV intake and the development of colitis and the improvement after discontinuation, an association seems not unlikely. Different mechanisms of action could be implicated.

A first possibility is the occurrence of a hypersensitivity syndrome, as described previously with other AEDs. This entity is characterized by fever, skin rash and involvement of multiple organ systems. The pathogenic mechanisms responsible for the development of hypersensitivity reactions are thought to include genetically determined abnormalities in enzymatic systems critical for the detoxification of metabolites of aromatic AEDs.[25,26] Colitis may be part of this AED-related hypersensitivity syndrome.[27] Because of the lack of other suggestive symptoms besides colitis this hypersensitivity syndrome is not the most likely explanation.

Due to the specific pharmacokinetic profile of LEV, the risk of drug interactions is very low. The major metabolic pathway is not dependent on the hepatic cytochrome P450 system and LEV does not inhibit or induce hepatic enzymes to produce clinically relevant interactions. It is not appreciably protein-bound nor does it affect the protein binding of other drugs. Thus, because of its minimal protein binding and lack of hepatic metabolism, the risk of drug pharmacokinetic drug interaction is very low.[16,28–31]

Another hypothesis may be that the association of carbamazepine with LEV could be the underlying cause. Earlier case reports have illustrated a drug-induced enterocolitis caused by carbamazepine.[32,33] In a recent article, Sisodiya et al. describes four patients with severe refractory epilepsy in whom introduction of LEV led to disabling symptoms compatible with carbamazepine toxicity requiring either carbamazepine dose reduction or LEV withdrawal. As carbamazepine and carbamazepine-epoxide blood levels were not altered during LEV co-medication, a pharmacodynamic interaction was suggested.[34] Adding lamotrigine to carbamazepine can also increase carbamazepine-related side effect without changes in carbamazepine or epoxide blood levels.[35] While a mild presentation of carbamazepine-induced colitis is not completely excluded in our patients, their symptoms subsided when the dose of LEV was tapered and the dose of carbamazepine remained unchanged, making this an unlikely hypothesis.

Finally, especially in view of the bloody stool reported in the second case report, haematological considerations have to be taken into account. In the past, the relationship between haematological side effects and treatment with various AEDs has been made.[36] For instance, valproate can cause direct bone marrow suppression leading to aplastic anaemia or peripheral cytopenia affecting one or more cell lines. A reported bleeding diathesis associated with valproate use may include thrombocytopenia, abnormal platelet function, and acquired von Willebrand disease type I.[37–39] Also felbamate, phenytoin and carbamazepine occasionally cause serious haematological disorders.[40–42]

Recently a case has been reported of a possible increased diathesis in patients undergoing resective surgery for refractory epilepsy who were treated with LEV.[22] The authors suggested that LEV treatment could be associated with haemorrhagic complications of epilepsy surgery more frequently than expected. They also hypothesized that LEV may have a subtle effect on megakaryocytes, producing a previously unappreciated bleeding diathesis.[22] Another recently published case report described a worsening of an immune thrombocytopenia during monotherapy with LEV.[43]

Both piracetam and LEV are pyrrolidone derivatives that share similar chemical structures but have distinct pharmacological profiles and consequently different clinical uses.[6] Piracetam is known to have important haemorrheological and antithrombotic properties that are very useful in the treatment of stroke. It increases the deformability of the erythrocyte membrane and decreases platelet aggregation in patients with increased platelet aggregability,[44–46] for example, in sickle cell anaemia. Although not demonstrated in the literature previously, it is therefore not unlikely that LEV may

have some impact on erythrocytes or platelets and their precursors, and exert haematological adverse events via this mechanism. In the present cases, there is however no clear-cut evidence to consider an underlying haematological aetiology for the punctate colitis.

Despite extensive experimental and clinical investigations concerning descriptions of the antiepileptic action of LEV, the exact mechanism of its action is still unknown. The existing experimental data do not allow attribution to any of the three main mechanisms currently accepted for the established AEDs: conventional GABA-ergic facilitation or inhibition of either Na^+ or low-voltage-activated Ca^{2+} currents. Recently, a study provided evidence that LEV selectively inhibits N-type calcium channel of pyramidal hippocampal neurons, suggesting the evidence of a subtype of N-type channels sensitive to LEV, possibly involved in its antiepileptic action.[47] Further elucidation of its mechanism of action may also shed more light on its side effect profile.

CONCLUSION

In view of the close temporal relationship between LEV intake and development of colitis, the improvement after discontinuation of LEV, and despite the fact that only a control colonoscopy could prove the regression of colitis, these case-reports suggest that colitis may be a possible and previously undescribed adverse effect of LEV.

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